General

Guideline Title

Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update.

Bibliographic Source(s)

Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, Smith TJ, Strawn JR, Trent D, Johnson DH. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2015 Oct 20;33(30):3488-515. PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G, American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009 Dec 20;27(36):6251-66. [157 references]

Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pao W, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G. 2011 focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2011 Oct 1;29(28):3825-31. [18 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence Based, Formal Consensus, Informal Consensus, No Recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Clinical Question A1

Which patients with stage IV non-small-cell lung cancer (NSCLC) should be treated with chemotherapy?

Recommendation A1.a

For patients with performance status (PS) of 0 or 1, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications

to platinum therapy. Chemotherapy may also be used to treat selected patients with PS 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Recommendation A1.b

Because there is no cure for patients with stage IV NSCLC, early concomitant palliative care assistance has improved the survival and well being of patients and is therefore recommended (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Clinical Question A2

What is the most effective first-line therapy for patients with stage IV NSCLC with non-squamous cell carcinoma (NSCC), negative or unknown epidermal growth factor receptor (*EGFR*)-sensitizing mutation and anaplastic lymphoma kinase (*ALK*) gene rearrangement status, and PS 0 to 1 or possibly PS 2?

Recommendation A2

For patients who have the characteristics described in Clinical Question A2 and who have nonsquamous histology, the following options are acceptable:

- Cisplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - Cisplatin plus docetaxel (U. S. Food and Drug Administration [FDA]-approved combination; http://www.cancer.gov)
  - Cisplatin plus paclitaxel (FDA-approved combination; http://www.cancer.gov)
  - Cisplatin plus pemetrexed (FDA-approved combination; http://www.cancer.gov)
  - Cisplatin plus vinorelbine (FDA-approved combination; http://www.cancer.gov)
- Carboplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - Carboplatin plus albumin-bound (nab)–paclitaxel (FDA approved combination; http://www.cancer.gov)
  - Carboplatin plus paclitaxel (FDA-approved combination; http://www.cancer.gov)
  - Carboplatin plus pemetrexed
  - Carboplatin plus docetaxel
- Nonplatinum doublets (type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: weak)

Clinical Question A2.a

What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status, NSCC, and no contraindications to bevacizumab?

Recommendation A2.a.1

For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS >1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (no change since 2011; type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation A2.a.2

There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab.

Clinical Question A2.b

What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, NSCC, and negative or unknown *EGFR*-sensitizing mutation and *ALK* gene rearrangement status?

Recommendation A2.b

In the context of shared decision making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2 (Chemotherapy: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: weak; Palliative care: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).

Clinical Question A3

What is the most effective first-line therapy for patients with stage IV NSCLC with SCC, negative or unknown *EGFR*-sensitizing mutation and *ALK* gene rearrangement status, and PS 0 to 1 or possibly PS 2?

Recommendation A3

Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options:

- Cisplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - Cisplatin plus docetaxel (FDA-approved combination; http://www.cancer.gov)
  - Cisplatin plus gemcitabine (FDA-approved combination; http://www.cancer.gov)
  - Cisplatin plus paclitaxel (FDA-approved combination; http://www.cancer.gov)
  - Cisplatin plus vinorelbine (FDA-approved combination; http://www.cancer.gov)
- Carboplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - Carboplatin plus gemcitabine
  - Carboplatin plus paclitaxel (FDA-approved combination; http://www.cancer.gov)
  - Carboplatin plus nab-paclitaxel (FDA-approved combination; http://www.cancer.gov)
  - Carboplatin plus docetaxel
- Nonplatinum doublets (type: evidence based, benefits outweigh harms; evidence quality: low; strength of recommendation: weak)

Clinical Question A3.a

What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status, SCC, and PS 2?

Recommendation A3.a

In the context of shared decision making, combination chemotherapy, single-agent chemotherapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a. (Chemotherapy: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: weak. Palliative care: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong.)

Clinical Question A4

What is the most effective first-line therapy for patients with stage IV NSCLC with an *EGFR*-sensitizing mutation and PS 0 to 1 or possibly PS 2?

Recommendation A4

If patients have stage IV NSCLC and a sensitizing *EGFR* mutation, first-line afatinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong), erlotinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong), or gefitinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong) is recommended.

Clinical Question A5

What is the most effective first-line therapy for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0 to 1 or possibly PS 2?

Recommendation A5

If patients have stage IV NSCLC and *ALK* rearrangements, first-line crizotinib is recommended (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Clinical Question A6

What is the most effective first-line therapy for patients with stage IV NSCLC with *ROS1* rearrangement, no *ALK* gene rearrangement, negative or

unknown *EGFR*-sensitizing mutation status, and PS 0 to 1 or possibly PS 2?

Recommendation A6

If patients have stage IV NSCLC with *ROS1* rearrangement, single-agent crizotinib is recommended, because it has shown some results indicating improved response rate and duration of response (type: informal consensus, benefits outweigh harms; evidence quality: low; strength of recommendation: weak).

Clinical Question A7

What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status and large-cell neuroendocrine carcinoma?

Recommendation A7

Patients with large-cell neuroendocrine carcinoma may receive the same treatment as other patients with NSCC or treatment with etoposide in platinum combinations (type: informal consensus, benefits outweigh harms; evidence quality: low; strength of recommendation: weak).

Clinical Question A8

What is the best chemotherapy for treatment of the elderly with stage IV NSCLC?

Recommendation A8

Decisions on the selection of chemotherapy should not be made or altered based on age alone (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Clinical Question A9

What is the optimal treatment for patients with stable disease or response after four cycles of cytotoxic chemotherapy?

Recommendation A9

In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is stable but not responding to treatment; two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease or response after four cycles of a first-line pemetrexed-containing regimen, continuation maintenance treatment with pemetrexed is recommended. For patients with stable disease or response after four cycles of a regimen that did not include a pemetrexed-containing combination, alternative single-agent chemotherapy, such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients, or a break from cytotoxic chemotherapy with initiation of second-line chemotherapy at disease progression may be recommended (addition of pemetrexed: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Clinical Question B1

What is the most effective second-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status and NSCC?

Recommendation B1

For patients with advanced NSCLC, NSCC, negative or unknown *EGFR/ALK* status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Clinical Question B2

What is the most effective second-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status and SCC?

Recommendation B2

For patients with advanced NSCLC, SCC, negative or unknown *EGFR/ALK* status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, docetaxel, erlotinib, or gefitinib is acceptable as second-line therapy (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Clinical Question B3.a

What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation who received a first-line EGFR tyrosine kinase inhibitor (TKI) and experienced disease progression?

Recommendation B3.a

For patients with a sensitizing *EGFR* mutation who did not respond to a first-line EGFR TKI, combination cytotoxic chemotherapy is recommended (Recommendation A2), following the first-line recommendations for patients with NSCC (type: informal consensus, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).

Clinical Question B3.b

What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation who received a first-line EGFR TKI and experienced disease progression after an initial response?

Recommendation B3.b

Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or another EGFR TKI as second-line therapy (type: informal consensus, balance of benefits and harms; evidence quality: low; strength of recommendation: weak).

Clinical Question B4

What is the most effective second-line therapy for patients with stage IV NSCLC with *ALK* rearrangement with progression after first-line crizotinib?

Recommendation B4

Patients whose tumors have *ALK* rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting (Chemotherapy: type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong; Ceritinib: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Clinical Question B5

What is the optimal second-line treatment for elderly patients with stage IV NSCLC?

Recommendation B5

The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. This recommendation has not changed. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.

Clinical Question C

Is there a role for third-line therapy or beyond in the treatment of stage IV NSCLC?

Recommendation C1

When disease progresses during or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib (no change).

Recommendation C2

Data are not sufficient to make a recommendation for or against using cytotoxic drugs as third-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care (no change from previous recommendations).

Definitions

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement (see the "Availability of Companion Documents" field).
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the

Rating for Strength of Recommendation	Definition
	guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Clinical Algorithm(s)

An algorithm titled "Stage IV NSCLC Treatment Algorithm" is available from the American Society of Clinical Oncology (ASCO) Web site .

Scope

Disease/Condition(s)

Stage IV non-small-cell lung cancer (NSCLC)

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Internal Medicine

Medical Genetics

Oncology

Intended Users

Physicians

Guideline Objective(s)

To provide evidence-based recommendations to update the American Society of Clinical Oncology guideline on systemic therapy for stage IV non-small-cell lung cancer (NSCLC)

Target Population

Patients with stage IV non-small-cell lung cancer (NSCLC)

Interventions and Practices Considered

1. Consideration of patient performance status (PS) when recommending cytotoxic chemotherapy
2. First-line chemotherapy
    - Cisplatin-based combinations (docetaxel, pemetrexed, gemcitabine, paclitaxel, or vinorelbine)
    - Carboplatin-based combinations (albumin-bound [nab], paclitaxel, gemcitabine, pemetrexed, or docetaxel)
    - Nonplatinum doublets
    - Bevacizumab added to carboplatin-paclitaxel
    - Pemetrexed in combination with bevacizumab/carboplatin (insufficient evidence to recommend)
    - Combination therapy, single-agent chemotherapy, or palliative therapy alone
    - Afatinib, erlotinib, or gefitinib as options in patients with a sensitizing epidermal growth factor receptor (*EGFR*) mutation
    - Crizotinib in patients:
        - With or without anaplastic lymphoma kinase (*ALK*) gene rearrangement
        - With *ROS1* rearrangements
        - Negative or unknown *EGFR*-sensitizing mutation status
    - Etoposide in platinum combinations in patients with large cell neuroendocrine carcinoma
3. Second-line chemotherapy
    - Docetaxel, erlotinib, gefitinib, or pemetrexed
    - Switching to cytotoxic chemotherapy or another EGFR tyrosine kinase inhibitor (TKI)
    - Ceritinib (in patients who had received crizotinib in the first line)
4. Third-line chemotherapy
    - Erlotinib
    - Cytotoxic drugs (insufficient evidence to make a recommendation)
5. Considerations for elderly patients (treatment decisions not to be made based on age alone)

Major Outcomes Considered

- Survival rates (disease-free, progression-free, overall)
- Adverse events
- Time to progression
- Health-related quality of life
- Symptom relief
- Response rate
- Toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The PubMed database was searched for evidence reporting on outcomes of interest, published from January 2007 to February 2014 for non–switch maintenance questions and from June 2009 to February 2014 for switch maintenance questions. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria: (1) population of patients with stage IV non-small-cell lung cancer (NSCLC) (many trials also included patients with stage IIIB NSCLC), and (2) fully published presentations of English-language reports of phase III randomized controlled trials (RCTs).

Articles were excluded from the systematic review if they were: (1) meeting abstracts not subsequently published in peer-reviewed journals (with one exception made for 2014 American Society of Clinical Oncology [ASCO] abstract presenting only phase III data on agent recently approved by the US Food and Drug Administration [FDA]); (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3)

published in a language other than English.

See the Data Supplement (see the "Availability of Companion Documents" field) for additional details on the literature search strategy, including search terms used.

Number of Source Documents

A total of 87 publications concerning 73 phase III randomized control trials (RCTs) met the systematic review eligibility criteria and form the evidentiary basis for the guideline recommendations.

Also see the Data Supplement (see the "Availability of Companion Documents" field) for a Quality of Reporting of Meta-analyses (QUOROM) diagram detailing the literature search results.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by one American Society of Clinical Oncology (ASCO) staff reviewer in consultation with the Steering Committee. Data were extracted by one staff reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary. Evidence tables are provided in the original guideline document and/or in Data Supplements 1 and 2 (see the "Availability of Companion Documents" field).

Study Quality Assessment

Study quality was formally assessed for the randomized controlled trials (RCTs) directly relevant to current recommendations. Quality assessment of studies not directly cited in support of recommendations is available in the Data Supplement. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources generally indicating an intermediate to high potential risk of bias for most of the identified evidence. Some factors varied between studies, lowering the comparability of the results. The "Rating Scheme for the Strength of the Evidence" field provides definitions of ratings for overall potential risk of bias.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee (CPGC) convened an Update Committee with multidisciplinary representation in medical oncology, nuclear and radiation oncology, surgical oncology, pathology, community oncology, patient/advocacy representation, and guideline implementation. The Update Committee was led by two Co-Chairs who had primary responsibility for the development and timely completion of the guideline. For this guideline, the Co-Chairs selected two additional members from the Update Committee to form a Steering Committee to assist in the development and review of the guideline drafts. Update Committee members are listed in Appendix Table A1 of the original guideline document.

Guideline Development Process

The Update Committee met by webinar on several occasions and corresponded frequently through e-mail; progress on guideline development was driven primarily by the Co-Chairs along with ASCO staff. The purpose of the meetings was for members to contribute content, provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Update Committee participated in the preparation of the draft guideline document, which was then disseminated for external review and submitted to the *Journal of Clinical Oncology* (*JCO*) for peer review and consideration for publication. All ASCO guidelines are reviewed and approved by the ASCO CPGC prior to publication.

Development of Recommendations

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software™. This method helps guideline panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.

Rating Scheme for the Strength of the Recommendations

Guide for Types of Recommendations

Type of Recommendation	Definition
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Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Members of the Update Committee were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology* (*JCO*) editorial review and consideration for publication. All American Society of Clinical Oncology

(ASCO) guidelines are ultimately reviewed and approved by the Update Committee and the ASCO Clinical Practice Guideline Committee (CPGC) before publication.

The CPGC approved this guideline on February 27, 2015.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate chemotherapy and biologic therapy in patients with stage IV non-small-cell lung cancer (NSCLC)

Potential Harms

Table 4 in the original guideline document lists selected adverse events from the first-line trials that reported them. Twenty-four trials reported significant differences. Table 5 in the original guideline document lists selected adverse events from the second-line trials that reported them.

Contraindications

Contraindications

Toxicity concerns, particularly major bleeding complications, are relative contraindications to the use of bevacizumab in patients with squamous-cell carcinoma.

Qualifying Statements

Qualifying Statements

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- Refer to the "Health Disparities", "MCCS" and "Limitations of the Research" sections in the original guideline document for additional qualifying information.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Implementation

American Society of Clinical Oncology (ASCO) guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners, survivors of cancer, and caregivers and the need to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and are also often published in *Journal of Clinical Oncology* (*JCO*) and *Journal of Oncology Practice*.

For information on the ASCO implementation strategy, please see the ASCO Web site .

Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, Smith TJ, Strawn JR, Trent D, Johnson DH. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2015 Oct 20;33(30):3488-515. PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

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American Society of Clinical Oncology (ASCO)

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Update Committee of the American Society of Clinical Oncology NSCLC Expert Panel

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Financial Disclosures/Conflicts of Interest

The Update Committee was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at http://www.asco.org/rwc). Members of the Update Committee completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with these procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I=Immediate Family Member, Inst=My Institution. Relationships may not relate to the subject matter of

this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Gregory A. Masters: No relationship to disclose

Sarah Temin: No relationship to disclose

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Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G, American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009 Dec 20;27(36):6251-66. [157 references]

Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pao W, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G. 2011 focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2011 Oct 1;29(28):3825-31. [18 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site.

Availability of Companion Documents

The following are available:

- Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2015. 16 p. Available from the American Society of Clinical Oncology (ASCO) Web site .
- Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2015. 122 p. Available from the ASCO Web site .
- Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2015. 30 p. Available in PowerPoint and PDF format from the ASCO Web site.
- Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2015. 7 p. Available from the ASCO Web site .
- Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Decision aid set. Alexandria (VA): American Society of Clinical Oncology; 2015. 26 p. Available from the ASCO Web site .

Patient Resources

The following is available:

- Systemic therapy for stage IV non-small cell lung cancer. Patient information. 2015 Aug 31. Available from the Cancer.Net Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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